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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/202,549	10/12/1999	PHILIP N. TSICHLIS	FCCC96-11	3050

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EXAMINER	
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ART UNIT	PAPER NUMBER
1636	18

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Please find below and/or attached an Office communication concerning this application or proceeding.

Application No.	Applicant(s)
09/202,549	TSICHLIS ET AL.
Examiner	**Art Unit**
Katharine F. Davis	1636

Office Action Summary

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 December 2001*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) *12-20* is/are withdrawn from consideration.

5)☒ Claim(s) *2-6, 9-11 and 21-24* is/are allowed.

6)☒ Claim(s) *7,8 and 25* is/are rejected.

7)☒ Claim(s) *1 and 8* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 5.
4)☐ Interview Summary (PTO-413) Paper No(s). _____.
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other:

DETAILED ACTION

This Office Action is in response to the application filed on October 12, 1999 and to the Response to Restriction Requirement filed on December 31, 2001. Claims 1-25 are pending in the instant application.

Election/Restrictions

Applicant's election without traverse of Group I (claims 1-11 and 21-25) in Paper No. 17 is acknowledged. Claims 12-20 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non elected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 17. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Specification

In the Brief Description of the Drawings section each panel or drawing containing multiple panels must be referred to as a separate figure. The first line of each description must refer to each separate figure (*e.g.*, Figures 2A-2E). Correction is required for Figures 2-4.

Sequences appearing in the specification and/or drawings must be identified by a sequence identifier in accordance with 37 C.F.R. 1.821(d). Applicant must provide an appropriate amendment to the instant specification indicating SEQ ID NOS for the sequences presented at page 23, Table II.

Claim Objections

Claims 1 and 8 are objected to because of the following informalities: Claim 1 recites the abbreviation "Gfi-1". An abbreviation should be defined upon first appearance in the claims. Claim 8 recites the sequence of SEQ ID NO: 2. The sequence appears to be missing a "T" at the fifth position. Appropriate correction is required for claims 1 and 8.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 25 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 25 is drawn to a method of treating a pathological condition related to the expression of an aberrant gene, said method which comprises administering to a patient in need of said treatment a pharmaceutical preparation comprising an expression vector that includes a non-aberrant counterpart of said aberrant gene and an operatively linked promoter comprising at least one mutated binding site for a Gfi-1 transcription repressor, said mutated binding site comprising a mutation which hinders or prevents binding of said Gfi-1 repressor to said site.

The following factors have been considered in formulating this rejection (*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988)): the breadth of the claims, the nature of the

invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

These **Wands factors** have been considered in determining that the specification does not enable the skilled artisan to make and use the claimed invention. This determination is based on several factors which, when considered together, illustrate that the art of *in vivo* gene delivery and expression (i.e. gene therapy) is in its infancy and highly unpredictable. The discussion will also be based on references whose teachings show that despite a tremendous amount of experimentation by highly skilled artisans, that in the field of *in vivo* gene delivery and expression, there remain significant hurdles and a high level of unpredictability. In the face of art-recognized hurdles and unpredictability, the specification must therefore include sufficient detailed teachings to enable the skilled artisan to navigate the art-recognized pitfalls and surmount the hurdles known in the art to make and use the invention as claimed (claim 25).

The breadth of the claim. Claim 25 is extremely broad in that it is drawn to any pathological condition, any aberrant gene and any expression vector delivered to a patient by any mode of administration.

The nature of the invention. The nature of the invention is a gene therapy method used to treat a pathological condition in a patient caused by expression of an aberrant gene.

The skill of the ordinary practitioner in the art. The skill of those practicing gene therapy is very high requiring expertise in both clinical and basic science.

The state of the prior art and the predictability or unpredictability of the art. The following references are cited herein to illustrate the state of the art of gene therapy as recently as the winter of 2001.

In theory, gene therapy is simple: replace the defective genetic component(s) and the disease dissipates. However in practice, gene therapy has yet to fulfill the theoretical expectations (see Hollon, editorial from Nature Medicine 6:1-2 January 2000, especially paragraph 4, column 1). Palù *et al.* (Journal of Biotechnology 68:1-13, 1999) reports that "Although gene transfer into humans has been demonstrated in several clinical trials, with more than 300 currently underway worldwide, there is still no single outcome that undoubtedly showed a consistent benefit for the patient" (see abstract).

Several major obstacles to the success of gene therapy have emerged: efficient transfer to target cells with sustained expression, quantitative transfer sufficient for therapeutic benefit, efficient production of appropriate vectors, selective and regulated transfer to target cells (especially in the case of malignant disease and AIDS), toxicity (immunogenicity) of vectors, and the unpredictable parallels of animal models to human beings.

Anderson (Nature 392 Suppl:25-30 1998) states "...the efficiency of gene transfer and expression in human patients is, however, still disappointingly low." (see page 25, column 1)

Viral vectors can only be produced in living systems that are not suited to high scale industrial production. It is also difficult to produce such vectors in high enough titers to infect the possible billions of affected cells in the body of a human being which would require transduction with and expression of the transgene encoded by the vector for therapeutic benefit. Viral vectors also need to be designed according to the cell type that they will be used to infect utilizing

knowledge of both cell specific receptors and regulation of gene expression to achieve targeting and sustained expression. (see page 5 of Rochlitz (Swiss Medical Weekly 131(1-2):4-9 January 2001) for a discussion of viral vectors).

Verma *et al.* (Nature 389:239-242 1997) indicates that a gene therapy protocol using naked DNA or an admixture of DNA with a transfection facilitating agent (such as a lipid) exhibits the problems of inefficient integration and a short duration of expression of the transfected DNA (see Table 2, page 242).

The art reports difficulty in drawing parallels with gene therapy protocols in animal models to gene therapy protocols in a clinical setting with human patients. Fox (American Society for Microbiology News 66(2) on-line journal, February 2000) discusses the medical complications that developed in mice and primates (blood clotting, liver damage, death) as a result of testing with an adenoviral vector used in the clinical trial that resulted in the death of Jesse Gelsinger (a participant in a gene therapy clinical trial at the University of Pennsylvania). These models did not provide any warning of the specific complications that were fatal to Gelsinger (the cause of death in the laboratory animals was not the same as the cause of death in the human patient, see page 2, last two paragraphs). See also Hollon for the discussion of the protocol in which Jesse Gelsinger was involved.

Anderson concludes with "...we still lack a basic understanding of how vectors should be constructed, what regulatory sequences are appropriate for which cell types, how *in vivo* immune defenses could be overcome, and how to manufacture efficiently the vectors that we do make(see page 30, conclusions).

A year later the conclusions of Palù *et al.* illustrate that the obstacles to gene therapy still have not been overcome. "The main, real obstacle to the development of gene therapy as a powerful therapeutic tool remains the targeted long-term regulated expression of the transgene." (see page 10) Palù *et al.* suggests further to echo Anderson that what is needed to overcome the obstacles to gene therapy is improved knowledge of vector construction and manufacture with increased knowledge of vector targeting and cell-specific gene regulation (see pages 10-11).

These articles illustrate and support the assertion that the art of *in vivo* gene therapy is still in its infancy (see Rochlitz, abstract) despite an enormous body of work by highly skilled artisans. The cited references also show that the art is highly unpredictable and that the art recognizes a number of fundamental stumbling blocks to gene transfer. There is a lack of conclusive evidence that gene therapy protocols are successful in the treatment of human disease. Thus, the effectiveness of a new protocol can not be predicted in the absence of prior documented success of similar protocols.

While these references acknowledge the usefulness of gene therapy and the possibility of developing efficacious strategies in the future, they also illustrate that there are numerous obstacles to successful gene therapy which current methods still must overcome. Accordingly, the disclosed utilities of the present specification which are drawn to gene therapy methods are credible. The present rejection, therefore is not for lack of utility, but rather for lack of enablement for methods other than those limited to *in vitro* methods.

The amount of direction or guidance presented in the specification and the presence or absence of working examples. Applicant has not provided guidance in the specification toward specific gene transfer protocols which would avoid the technical obstacles recognized in

the art, as described above. The instant specification describes no examples in which an expression vector as recited by claim 25 is used to treat a pathological condition in a patient caused by expression of an aberrant gene.

The quantity of experimentation. The references cited above describe a sizeable number of studies, with only hints of therapeutic benefits--because of the obstacles to gene delivery or transfer. Despite the tremendous amount of experimentation already devoted to developing gene transfer methods, significant barriers still exist even after Applicants' filing date. This indicates that thus far, no amount of experimentation has resulted in a clearly successful and/or predictable gene transfer method.

It has been established that a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion. Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable the skilled artisan to understand and carry out the invention. It is true that a specification need not disclose what is well known in the art. That general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, in the above discussion, it has been established that there is very little in the art of gene transfer that is well known and predictable.

To attempt to practice the claimed invention one of skill in the art would turn to the specification for guidance in practicing the invention. As set forth above, however, the specification lacks sufficient guidance to surmount the technical difficulties recognized in the art.

Another source of guidance for one skilled in the art, the prior art, again for reasons set forth above, also lacks solutions to overcome the considerable list of obstacles recognized in the field of gene therapy. In the absence of instruction from the specification and the prior art, one of skill in the art would resort to experimentation to navigate the obstacles to practicing the claimed invention. Again, as established above, solutions to these technical problems have been elusive despite an enormous amount of experimentation due to a number of factors, including the unpredictable nature of the art of gene transfer and therapy. Such unpredictability would warrant even more experimentation, with no true expectation of a measure of success. This is analogous to searching for a needle in a haystack without knowing that the haystack even has a needle.

Based on the above presented discussion of the broad scope of the claims, the nature of the invention, the skill of those in the art, the unpredictability of the area of the invention, the lack of sufficient guidance or working examples in the specification and the quantity of experimentation necessary, it would clearly require undue experimentation by one of skill in the art to use the claimed gene therapy protocol to treat a pathological condition in a patient caused by expression of an aberrant gene.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 7 and 8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 7 and 8 recite the phrase "...homologous with a sequence comprising..." Are applicants claiming percent homologies with any sequence comprising SEQ ID NO: 2? The metes and bounds of the claimed sequence are undetermined and therefore indefinite. Amending the claims to recite "...homologous with a sequence **consisting of**..." would overcome this rejection.

Conclusion

Claims 7, 8 and 25 are rejected. Claims 1 and 8 are objected to for minor informalities. Claim 2-6, 9-11 and 21-24 will be allowable upon correction of the objections to the specification. Claims 1-11 and 21-25 are free of the prior art. The closest prior art of record with regard to claim 1-11 and 21-25 is Gilks *et al.* (Molecular and Cellular Biology 13(3):1759-1768 1993, IDS reference) and Gilks *et al.* (Endocrinology 136(4):1805-1808 1995, IDS reference). These references disclose that Gfi-1 was known in the art as a transcription repressor however these references do not teach or suggest the use of mutated binding sites for Gfi-1 as a method to increase transcription. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Katharine F. Davis whose telephone number is (703)

605-1195 with direct desktop RightFax (703) 746-5199. The examiner can normally be reached on Monday-Friday (8:30am-5:00pm). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on (703) 305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 305-1935 for After Final communications. Any inquiry of a general nature or any inquiry concerning the formalities of this application should be directed to Patent Analyst Dianiece Jacobs whose telephone number is (703) 305-3388.

Katharine F. Davis
January 13, 2002

DAVID GUZO
PRIMARY EXAMINER